

**PRESCRIBING INFORMATION
PRODUCT MONOGRAPH**

ZARONTIN*

**Ethosuximide Capsules USP
250 mg Capsules**

**Ethosuximide Oral Solution B.P.
250 mg/5 mL (50 mg/mL) Solution**

ANTICONVULSANT



8250 Décarie Blvd, suite 110
Montréal, QC
Canada, H4P 2P5

DATE OF PREPARATION:

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Control No. 162469

PRESCRIBING INFORMATION**ZARONTIN*****Ethosuximide Capsules USP
250 mg Capsules****Ethosuximide Oral Solution B.P.
250 mg/5 mL (50 mg/mL) Solution****THERAPEUTIC CLASSIFICATION**

Anticonvulsant

ACTION AND CLINICAL PHARMACOLOGY

ZARONTIN (ethosuximide) is completely and rapidly absorbed from the gastrointestinal tract. Peak plasma levels occur 1 to 7 hours after a single oral dose. Ethosuximide is not significantly bound to plasma proteins; therefore, the drug is present in saliva and CSF in concentrations approximately equal to that of the plasma. Therapeutic concentrations are in the range of 280 to 710 $\mu\text{mol/L}$ (40 to 100 :g/mL). Ethosuximide is extensively metabolized to at least 3 plasma metabolites. Only 12 to 20% of the drug is excreted unchanged in the urine. The elimination half-life for the drug is 40 to 60 hours in adults and 30 hours in children.

INDICATIONS AND USAGE

ZARONTIN (ethosuximide) is used for the control of absence (petit mal) epilepsy.

CONTRAINDICATIONS

Ethosuximide should not be used in patients who are hypersensitive to succinimides or components of these products.

WARNINGS

Blood dyscrasias, including some with fatal outcomes, have been reported to be associated with the use of ethosuximide; therefore, periodic blood counts should be performed. Should signs and/or symptoms of infection (e.g., sore throat, fever) develop, blood count determinations should be considered at that point.

Ethosuximide is capable of producing morphological and functional changes in the animal liver. In humans, abnormal liver and renal function studies have been reported.

Administer ethosuximide with extreme caution to patients with known liver or renal disease. Periodic urinalysis and liver function studies are advised for all patients receiving the drug.

Cases of systemic lupus erythematosus have been reported with the use of ethosuximide. The physician should be alert to this possibility.

Pregnancy: Recent reports indicate an association between the use of anticonvulsant drugs and an elevated incidence of birth defects in children born to epileptic women taking such medication during pregnancy. The incidence of congenital malformations in the general population is regarded to be approximately 2%; in children of treated epileptic women this incidence may be increased 2 to 3 fold. The increase is largely due to specific defects, e.g., congenital malformations of the heart, and cleft lip and/or palate. Nevertheless, the great majority of mothers receiving anticonvulsant medications deliver normal infants.

Data are more extensive with respect to phenytoin and phenobarbital, but these drugs are also the most commonly prescribed anticonvulsants. Some reports indicate a possible similar association with the use of other anticonvulsants, including trimethadione and paramethadione. However, the possibility also exists that other factors, e.g., genetic predisposition or the epileptic condition itself may contribute to or may be mainly responsible for the higher incidence of birth defects.

Anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures, because of the strong possibility of precipitating status epilepticus with attendant hypoxia and risk to both the mother and the unborn child. With regard to drugs given for minor seizures, the risk of discontinuing medication

prior to or during pregnancy should be weighed against the risk of congenital defects in the particular case and with the particular family history.

Epileptic women of childbearing age should be encouraged to seek professional counsel and should report the onset of pregnancy promptly to their physician. Where the necessity for continued use of antiepileptic medication is in doubt, appropriate consultation might be indicated.

The preceding considerations should be borne in mind and ethosuximide should be used in women of childbearing potential only when the expected benefits to the patient warrant the possible risk to a fetus. Mothers receiving ethosuximide should not breast-feed their infants.

Suicidal Ideation and Behavior

Suicidal ideation and behavior have been reported in patients treated with antiepileptic agents in several indications.

All patients treated with antiepileptic drugs, irrespective of indication, should be monitored for sign of suicidal ideation and behavior and appropriate treatment should be considered.

Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behavior emerge.

An FDA meta-analysis of randomized placebo controlled trials, in which antiepileptic drugs were used for various indications, has shown a small increased risk of suicidal ideation and behavior in patients treated with these drugs. The mechanism of this risk is not known.

There were 43892 patients treated in the placebo controlled clinical trials that were included in the meta-analysis. Approximately 75% of patients in these clinical trials were treated for indications other than epilepsy and, for the majority of non-epilepsy indications the treatment (antiepileptic drug or placebo) was administered as monotherapy. Patients with epilepsy represented approximately 25% of the total number of patients treated in the placebo controlled clinical trials and, for the majority of epilepsy patients, treatment (antiepileptic drug or placebo) was administered as adjunct to other

antiepileptic agents (i.e., patients in both treatment arms were being treated with one or more antiepileptic drug). Therefore, the small increased risk of suicidal ideation and behavior reported from the metanalysis (0.43% for patients on antiepileptic drugs compared to 0.24% for patients on placebo) is based largely on patients that received monotherapy treatment (antiepileptic drug or placebo) for non-epilepsy indications. The study design does not allow an estimation of the risk of suicidal ideation and behavior for patients with epilepsy that are taking antiepileptic drugs, due both to this population being the minority in the study, and the drug-placebo comparison in this population being confounded by the presence of adjunct antiepileptic drug treatment in both arms.

Children: Safety and effectiveness in pediatric patients below the age of 3 years have not been established (see Dosage).

Occupational Hazards: Ethosuximide may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a motor vehicle or other such activity requiring alertness.

PRECAUTIONS

Ethosuximide, when used alone in mixed types of epilepsy, may increase the frequency of grand mal seizures in some patients.

As with other anticonvulsants, it is important to proceed slowly when increasing or decreasing dosage, as well as when adding or eliminating other medication. Abrupt withdrawal of anticonvulsant medication may precipitate absence (petit mal) status.

Drug Interactions: Since ethosuximide may interact with concurrently administered antiepileptic drugs, periodic serum level determinations of these drugs may be necessary (e.g., ethosuximide may elevate phenytoin serum levels and valproic acid has been reported to both increase and decrease ethosuximide levels).

Carcinogenicity, Mutagenesis, and Impairment of Fertility: There have been no adequate, well-controlled studies on the carcinogenicity, mutagenicity, or impairment of fertility of this product.

ADVERSE REACTIONS

Gastrointestinal: Gastrointestinal symptoms occur frequently and include anorexia, vague gastric upset, nausea and vomiting, cramps, epigastric and abdominal pain, weight loss, and diarrhea. There have been reports of gum hypertrophy and swelling of the tongue.

Hemopoietic: leukopenia, agranulocytosis, pancytopenia, aplastic anemia, with or without bone marrow suppression and eosinophilia.

Nervous system: Neurologic and sensory reactions reported during therapy with ethosuximide have included drowsiness, headache, dizziness, euphoria, hiccups, irritability, hyperactivity, lethargy, fatigue, and ataxia. Psychiatric or psychological aberrations associated with ethosuximide administration have included disturbances of sleep, night terrors, inability to concentrate, and aggressiveness. These effects may be noted particularly in patients who have previously exhibited psychological abnormalities. There have been rare reports of paranoid psychosis, increased libido, and increased state of depression with overt suicidal intentions.

Integumentary: Dermatologic manifestations which have occurred with the administration of ethosuximide have included urticaria, Stevens-Johnson syndrome, systemic lupus erythematosus, and pruritic erythematous rashes.

Genitourinary: microscopic hematuria, vaginal bleeding

Miscellaneous: myopia, hirsutism.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Overdose: Symptoms: Acute overdoses may produce nausea, vomiting, and CNS depression including coma with respiratory depression. A relationship between ethosuximide toxicity and its plasma levels has not been established. The therapeutic range is 280 to 710 :mol/L, although levels as high as 1,050 µmol/L have been reported without signs of toxicity.

Treatment: Treatment should include emesis (unless the patient is or could rapidly become obtunded, comatose, or convulsing) or gastric lavage, activated charcoal,

cathartics and general supportive measures. Hemodialysis may be useful to treat ethosuximide overdose. Forced diuresis and exchange transfusions are ineffective.

DOSAGE AND ADMINISTRATION

Initial dose: children aged 3 to 6 years, 250 mg daily; older patients, 500 mg daily in divided doses. The dose thereafter must be individualized according to response and tolerance. Medicament should be increased by small increments: e.g. increase daily dose by 250 mg every 4 to 7 days until control is achieved with minimal side effects. Daily dosage of 1 to 1.5 g in divided doses frequently controls seizures; however, it may be necessary to exceed this amount by slow increases and careful evaluation of patient's response. Dosage exceeding 1.5 g daily, in divided doses, should be administered only under the strictest supervision of the physician. The optimal dose for most children is 20 mg/kg/day. This dose has given average plasma levels within the accepted therapeutic range of 280 to 710 µmol/L (40 to 100 µg/mL). Subsequent dose schedules can be based on effectiveness and plasma level determinations.

Ethosuximide may be administered in combination with other anticonvulsants when other forms of epilepsy coexist with absence (petit mal). The optimal dosage for most children is 20 mg/kg/day.

AVAILABILITY

ZARONTIN (ethosuximide) capsules are available in the dosage strength of 250 mg per capsule. Nonmedicinal ingredients: polyethylene glycol, D&C Yellow No. 10, FD&C Red No. 3, gelatin, glycerin and sorbitol. Available in bottles of 100.

ZARONTIN (ethosuximide) oral solution (syrup). Each 5 mL contains 250 mg ethosuximide. Nonmedicinal ingredients: alcohol, citric acid anhydrous, FD&C Yellow No. 6, FD&C Red No. 3, flavoring agents, glycerin, purified water, saccharin sodium, sodium benzoate, sodium citrate, sucrose and vanillin. Alcohol: 3%. Energy: 62.76 kJ (15 kcal)/5 mL. Sodium: <1 mmol (6.7 mg)/5 mL. Gluten-, lactose-, parabens-, sulfite- and tartrazine-free. Available in bottles of 500 mL.

STABILITY AND STORAGE RECOMMENDATION

Store ZARONTIN (ethosuximide) capsules between 15 and 25°C and protect from heat.
Store syrup between 15 and 25°C and protect from freezing and light.

INFORMATION FOR THE PATIENT

Occupational Hazards: Ethosuximide may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a motor vehicle or other such activity requiring alertness; therefore the patient should be cautioned accordingly. Patients taking ethosuximide should be advised of the importance of adhering strictly to the prescribed dosage regimen. Patients should be instructed to promptly contact their physician if they develop signs and/or symptoms (e.g., sore throat, fever) suggesting an infection.

PHARMACEUTICAL INFORMATION**Drug Substance**

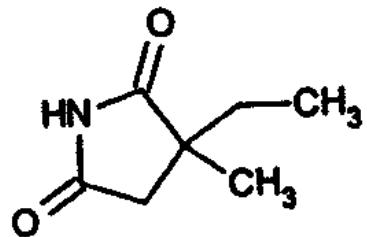
Proper Name: Ethosuximide

Chemical Name: 3-ethyl-3-methyl-2, 5-pyrrolidinedione, 3-ethyl-3-methyl-, (\pm)-.

Empirical Formula: C₇H₁₁NO₂

Molecular Weight: 141.17

Structural Formula:



IMPORTANT: PLEASE READ**CONSUMER INFORMATION****ZARONTIN®**

(Ethosuximide)

250 mg Capsules USP**or****Ethosuximide Oral Solution B.P.****250 mg/5 mL (50 mg/mL) Solution**

Read this information each time you refill your prescription in case new information has been added. This leaflet is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ZARONTIN®. Contact your doctor or pharmacist if you have any questions about this drug. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION**What the medication is used for:**

ZARONTIN® is used to control absence (petit mal) seizures.

What it does:

ZARONTIN® is an anti-epileptic drug. It is used to treat epilepsy. The exact mechanism of action is not entirely understood.

When it should not be used:

DO NOT TAKE ZARONTIN® if you have any of the following medical conditions:

- Known allergy to ethosuximide (Zarontin) or any component of this medication.
- Hypersensitivity to succinimides or components of these products.

What the medicinal ingredient is:

Ethosuximide

What the non medicinal ingredients are:

For the capsules: polyethylene glycol, D&C Yellow No. 10, FD&C Red No. 3, gelatin, glycerin and sorbitol.

For the oral solution: alcohol, citric acid anhydrous, FD&C Yellow No. 6, FD&C Red No. 3, flavoring agents, glycerin, purified water, saccharin sodium, sodium benzoate, sodium citrate, sucrose and vanillin.

What dosage forms it comes in:

Capsules; 250 mg

Oral solution: 250 mg/5ml

WARNING AND PRECAUTIONS

Before you use ZARONTIN talk to your doctor or pharmacist if you

- have liver or kidney disease
- have or have had depression, or mood problems
- have or had grand mal seizures or lupus
- have any other medical conditions
- are pregnant or plan to become pregnant. When pregnant women use anticonvulsant drugs such as ZARONTIN®, there may be a higher risk of birth defects in the baby. Tell your healthcare provider right away if you become pregnant while taking ZARONTIN®. You and your healthcare provider should decide if you should take ZARONTIN® while you are pregnant. Talk to your healthcare provider about registering with the North American Antiepileptic Drug Pregnancy Registry. The purpose of this registry is to collect information about the safety of medicines used to treat seizures during pregnancy. You can enroll in this registry by calling 1-888-233-2334. Information on the registry can also be found on the following website: <http://aedpregnancyregistry.org/>.
- are breast-feeding or plan to breast-feed. ZARONTIN passes into breast milk.

Some people have thoughts of suicide or hurting themselves while taking medications to prevent seizures such as ZARONTIN®. Talk to your doctor right away if this happens to you.

Driving and using machines: Before you perform tasks which may require special attention, wait until you know how you respond to ZARONTIN®.

This medication has been prescribed specifically for you. DO NOT give it to anyone else. It may harm them, even if their symptoms seem to be similar to yours.

Abnormal liver and renal function studies have been reported with the use of this medication. Your physician will perform periodic blood counts since presence of abnormal blood constituents or constituents in abnormal quantity that could lead to fatal outcomes have been reported to be associated with the use of ZARONTIN®.

INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. Tell your doctor or pharmacist about all the medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative medicines.

Do not start or stop other medicines without talking to your doctor, nurse, or pharmacist. The blood level of ZARONTIN® and any other antiepileptic drugs may need to be checked by a blood test.

Know the medicines you take. Keep a list of them with you to show your healthcare provider and pharmacist when you get a new medicine.

Drugs that may interact with ZARONTIN® include:

- Anticonvulsant (antiepileptic drugs) such as phenytoin, phenobarbital or valproic acid
- Lamotrigine, an anticonvulsant drug used in the treatment of epilepsy and bipolar disorder.

PROPER USE OF THIS MEDICATION

You should never discontinue this medication without consulting your physician. Some conditions may become worse when the drug is suddenly stopped. Your dose may need to be gradually decreased.

Take ZARONTIN® exactly as instructed by your doctor.

It is important to keep your appointments for medical checkups.

Dosage is individualised. Your doctor will start you on a low dose and slowly increase your dose. It may take several weeks or months to reach the best dose for you and to get the full benefit from this medication. To help you remember, use it at the same time(s) each day.

ZARONTIN® may be taken with or without food.

Usual adult dose:

Initial dosage for adult is one capsule twice daily. Dose may be increased gradually by physician to optimal dosage in order to control seizures with the least side effects.

Usual adult dose is 2 to 3 capsules twice daily.

If you are using the liquid form of this medication, carefully measure the dose using a special measuring device/spoon. Do not use a household spoon because you may not get the correct dose.

Usual Children Dose:

Not to be used by children younger than 3 years old.

Initial dose for children aged 3 to 6 years old is one teaspoonful per day (250 mg). Optimal dose for most children is 20 mg/kg/day.

If you are using the liquid form of this medication, carefully measure the dose using a special measuring device/spoon. Do not use a household spoon because you may not get the correct dose.

Missed Dose

Do not abruptly stop taking your medicine, because of the risk your epileptic seizures.

If a dose is missed, you should take it as soon as you remember. If it is near the time of the next dose, skip the missed dose and resume your usual dosing schedule. Do not double the dose to catch up.

Overdose

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:

- Nausea, diarrhea, vomiting, indigestion.
- Drowsiness, dizziness, lethargy, sedation
- Euphoria, hyperactivity

If any of these affects you severely, tell your doctor or pharmacist.

ZARONTIN® can cause abnormal urine and blood test results. Your doctor will decide when to perform urine and blood tests and will interpret the results.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
Symptom	talk to your physician or pharmacist right away		Seek emergency medical attention IMMEDIATELY
	Only in severe cases	In all cases	
Uncommon	Thoughts of suicide or hurting yourself	✓	
	Allergic reaction (symptoms include swelling in the eyes, lips, mouth, tongue, face and throat, itching, rash, hives)		✓
	Decreased platelets in the blood, fatigue, weakness, bleeding or bruising more easily than normal, nose bleeds	✓	
	Decreased white blood cells fatigue, fever, aches, pains and flu-like symptoms	✓	
	Psychotic disorders Hallucinations (hearing things that are not there), psychosis aggression	✓	
	Severe skin rash that causes blistering		✓
	Pain and inflammation of the joints	✓	
	Porphyria (abdominal pain, light sensitivity causing rashes, blistering or scarring of the skin, seizures, mental disturbances or nerve damage)		✓

Ataxia Lack of voluntary coordination of muscle movements	✓	
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This is NOT a complete list of side effects. If you develop any other symptoms while taking ZARONTIN®, see your health care provider.

HOW TO STORE IT

Do NOT keep outdated medicine or medicine no longer needed. Any outdated or unused medicine should be returned to your pharmacist.

Keep the capsules and the oral solution in a dry place at normal room temperature (15°C- 30°C) in the packaging that they come in. Protect from light and freezing.

Keep out of sight and reach of children.

MORE INFORMATION

This document plus the full product monograph prepared for health professionals can be found at <http://www.ECI2012.net> or by contacting the sponsor, ERFA Canada 2012 Inc. at 1-888-922-3133.

This leaflet was prepared by ERFA Canada 2012 Inc.

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REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

Report online at www.healthcanada.gc.ca/medeffect

Call toll-free at 1-866-234-2345

Complete a Canada Vigilance Reporting Form and:

- Fax toll-free to 1-866-678-6789, or
- Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701E
Ottawa, Ontario
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.